AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 07: Diabetes Mellitus

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 150 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the six topics for which (1) preliminary phase III data for drugs, at least phase II or equivalent data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled by May 15, 2014, in this priority area; *and* (3) we received five to eight sets of comments from experts between July 1, 2013, and May 23, 2014. (Twenty-two topics in this priority area were being tracked in the system as of May 15, 2014.) For this report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present five summaries on topics (indicated below by an asterisk) that emerged as having higher-impact potential on the basis of experts' comments and assessment of potential impact.

The material on interventions in this Executive Summary and report is organized alphabetically by disease state and then by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 07: Diabetes

Topic	High-Impact Potential
1. *Artificial pancreas device system (MiniMed 350G with Enlite low-glucose suspend system) for treatment of diabetes requiring exogenous insulin	High
2. Buccal insulin (Oral-lyn) for treatment of type 1 or type 2 diabetes	No high-impact potential at this time
3. *Degludec ultra-long-acting insulin (Tresiba) and degludec plus aspart (Ryzodeg) for treatment of type 1 or 2 diabetes	Lower end of the high-impact-potential range
4. *Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema	Lower end of the high-impact-potential range
5. *ITCA 650 (exenatide continuous subcutaneous delivery) for treatment of type 2 diabetes	Lower end of the high-impact-potential range
6. *Metabolic (bariatric) surgery for resolution of type 2 diabetes in mildly obese and nonobese patients	High

Discussion

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia (elevated blood sugar). Diabetes-associated hyperglycemia results from dysfunction in either insulin secretion

or insulin action or both. Most diabetes mellitus cases fall into one of two broad categories: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). According to a 2012 report from the U.S. Centers for Disease Control and Prevention (CDC), T1DM accounts for about 5% of all diagnosed cases and T2DM makes up the rest. The American Diabetes Association (ADA) fact sheet on diabetes reports that about 29.1 million children and adults in the United States, or 9.3% of the total population, have diabetes mellitus. About 21 million of these people have received a diagnosis of diabetes, but in the other 8.1 million, the disorder is undiagnosed. Furthermore, about 86 million people in the United States have prediabetes or are at risk of developing T2DM. ADA stated that clinicians diagnosed 1.7 million new cases of diabetes in U.S. people aged 20 years or older in 2012 (the most recent year for which statistics are available).

The Mayo Foundation for Medical Education and Research (MFMER) states that T1DM risk factors include family history of T1DM and presence of certain genetics, whereas T2DM risk factors include being overweight, having a body that primarily stores fat in the abdomen, having a family history of the disease, or having another form of diabetes mellitus such as prediabetes or gestational diabetes. Being African American, Hispanic, American Indian, or Asian American is also a risk factor for T2DM. According to CDC, diagnosed T2DM is seven times as prevalent in adults aged 65 years or older as in adults aged 20–44 years. MFMER recommends diabetes screening for overweight children and adults who have risk factors; adults older than age 45 years should undergo screening every 3 years. The latter recommendation is controversial; the U.S. Preventive Services Task Force concluded that the evidence was insufficient for recommending screening for adults with normal blood pressure.

T1DM results from an absolute deficiency of insulin secretion. ADA states that the disease is caused by destruction of the pancreatic beta cells and that this destruction is either immune mediated or idiopathic, with immune-mediated destruction accounting for the majority of cases. T1DM can occur at any age but is most often diagnosed in children, adolescents, or young adults. MFMER states that all patients with T1DM require insulin therapy.

T2DM hyperglycemia is a result of insulin resistance or a diminished response to insulin. ADA states that patients with T2DM also often have a relative insulin deficiency and may have an insulin secretory defect in conjunction with insulin resistance. T2DM was previously referred to as noninsulin-dependent diabetes; as that name suggests, patients often do not require insulin to survive.

Clinicians use one of three tests to diagnose diabetes mellitus: fasting plasma glucose test, oral glucose tolerance test, and casual plasma glucose level measurement. A fasting plasma glucose level of 126 mg/dL or more, an oral glucose tolerance test reading of 200 mg/dL or more, or a casual plasma glucose level of 200 mg/dL or more in conjunction with hyperglycemia symptoms all signal a diabetes diagnosis.

Additionally, a glycated hemoglobin (HbA_{1c}) test may be performed. This test indicates the patient's average blood sugar level for the previous 2 or 3 months. MFMER considers an HbA_{1c} level of 6.5% or higher on two separate tests to indicate a diagnosis of diabetes.

Diabetes mellitus treatment and management to prevent complications require patients to make a lifelong commitment to exercising regularly, maintaining a healthy weight, eating healthy foods, monitoring blood sugar, and, in some cases, taking insulin. According to MFMER, the primary treatment goal is to maintain blood sugar levels as close to normal as possible to delay or prevent complications.

After diagnosis and disease-type classification, patients undergo evaluation to detect complications, review glycemic control challenges, and establish treatment goals, including target HbA_{1c} levels. Patients receive a treatment plan and are taught how to self-manage day-to-day care. Clinicians generally encourage patients to achieve an HbA_{1c} level of 7% or lower because this value

has been shown to reduce diabetes-associated microvascular complications. However, targets are individualized according to clinician judgment about the optimal goal for a specific patient, taking into account the patient's medical characteristics and age.

For T2DM, several self-administered, oral antidiabetes agents, alone or in combination, are generally tried as first-line therapy. These include biguanides, sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and dipeptidyl peptidase-4 inhibitors. Many patients with T2DM do not meet treatment goals and require additional therapy with one of two types of injected antidiabetes agents: subcutaneous insulin or a glucagon-like peptide-1 (GLP-1) agonist. Insulin supplementation has become increasingly common with T2DM.

New treatments in development for diabetes focus on delaying disease onset in at-risk patients and improving diabetes management and treatment adherence. New drugs, technologies, and drug-delivery modalities are intended to optimize efficacy to enable patients to meet and maintain near-normal glycemia without acute excursions high or low (i.e., hyperglycemia, hypoglycemia), to improve patient adherence to treatment regimens, and to avoid weight gain and secondary complications (i.e., nephropathy, neuropathy, retinopathy).

Prior Potential High Impact Topics

The following two topics that have been previously designated as having high-impact potential have been archived since the December 2013 report period because they have timed out of the horizon scanning system.

- **Exenatide extended-release (Bydureon) for treatment of diabetes:** In the December 2013 report, commenters considered this intervention to be on the lower end of the high-impact-potential range. The U.S. Food and Drug Administration (FDA) approved exenatide extended-release in January 2012 for treating patients with T2DM. The topic has been archived from the horizon scanning system because it has diffused and has been available for more than 2 years.
- **Ranibizumab (Lucentis) for treatment of diabetic macular edema:** In the December 2013 report, commenters considered this intervention to be on the lower end of the high-impact-potential range. FDA approved ranibizumab in August 2012 for treating patients with diabetic macular edema. The topic has been archived from the horizon scanning system because it has widely diffused.

Eligible Topic Not Deemed High Impact

- **Buccal insulin (Oral-lyn) for treatment of type 1 or type 2 diabetes:** Buccal insulin (Generex Biotechnology Corp., Toronto, Ontario, Canada) is a fast-acting insulin that is sprayed in aerosol form on the inside of the cheek (buccal mucosa) to allow rapid absorption into bloodstream. Experts commenting on this intervention cited a limited amount of safety and efficacy data. In light of experts' comments, this topic is being tracked in the horizon scanning system, although for this report it was considered as not having high impact potential at this time.

Eligible Topics Deemed High Impact

The five topics deemed by commenters as having high-impact potential included devices, drugs, and procedures to treat diabetes mellitus and a treatment for a diabetes-related eye disorder, diabetic macular edema.

The devices are a product that is the first step toward realizing the goal of an artificial pancreas device system and a tiny subcutaneous insulin dispenser. The drug intervention combines long- and short-acting insulin. Another topic is bariatric surgery for individuals with diabetes who are not typically considered for the surgery because their body mass index is lower than 35. The intervention for diabetic macular edema combines a corticosteroid with a delivery device that is implanted in the eye and purported to deliver a steady flow of the drug over 2–3 years.

Artificial Pancreas Device Systems (MiniMed 530G with Enlite Low-Glucose Suspend System) for Treatment of Diabetes

- **Key Facts:** An artificial pancreas device system (APDS) consists of an external or implantable insulin pump, real-time continuous glucose monitor, and a small computing device with software and algorithms to detect glucose levels and coordinate appropriate insulin delivery. Many believe that the APDS will be the ideal management strategy for patients with diabetes who require intensive insulin therapy. Researchers and manufacturers are developing two types of systems: reactive and predictive low-glucose suspend systems. In reactive systems, patients or clinicians set a blood glucose threshold, and the pump automatically shuts off when that reading is reached. In predictive systems, the monitor uses control algorithms that predict when the patient's blood glucose is projected to decrease to a dangerously low level. Although many proof-of-concept studies of closed-loop systems (CLSs) have been performed and all the necessary component parts of a CLS exist, a truly portable CLS for routine use is likely several years from realization. This is because major advances in sensor technologies and artificial pancreas software algorithms are needed, as is a developer that integrates the disparate components into a single CLS. The Juvenile Diabetes Foundation has committed significant resources to developing a system, and several are in pilot studies. In November 2012, FDA issued guidance for developers titled, "The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems" to guide trial conduct and regulatory submissions.

  The MiniMed 530G with Enlite® sensor (Medtronic, Inc., Minneapolis, MN) is the first step toward a commercially available APDS. FDA approved the MiniMed 530G system for marketing on September 27, 2013. The system uses threshold-suspend automation, a feature intended to automatically stop insulin delivery (for up to 2 hours) when sensor glucose values reach a preset level and when the patient does not respond to the threshold suspend alarm. The indication is "for use by people with diabetes ages 16 and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin." This system is the first to be approved under FDA's new product classification, "OZO: Artificial Pancreas Device System, Threshold Suspend."

  Early reports of the pump system cost put the retail price at $7,350, with insured patients typically paying $500 to $1,200 out of pocket. Medtronic introduced the Path2System Program to aid adoption by existing pump users. According to the company, patients using the Paradigm® Revel™ Insulin Pump and Continuous Glucose Monitoring (CGM) system with a valid warranty are able to obtain the new MiniMed 530G system for $399 plus the cost of the Enlite starter kit. Patients' out-of-pocket costs for CGM vary according to their health plan coverage. The Path2System includes the MiniMed 530G insulin pump; Enlite training packet; MiniLink transmitter, charger and test plug; and Enlite Starter Kit. Many third-party payers cover the system according to its labeled indication for patients who meet criteria for an external insulin pump.

- **Key Expert Comments:** Overall, experts agreed on the need for systems that help patients achieve adequate glucose control. Most experts commenting on this intervention opined that it has the potential to improve patient health outcomes by reducing hypoglycemic episodes. Several experts commented that the intervention would significantly improve patient health outcomes in patients with hypoglycemia unawareness. Most experts commented that this intervention represents an important step towards a true APDS. However, experts cited the inability to address hyperglycemic episodes to be a limiting factor. Experts generally agreed that both patients and clinicians would adopt this intervention. However, some experts cited cost, insurance coverage, and device training to be potential barriers to acceptance.
- **Potential for High Impact**: High

Degludec Ultra-Long-Acting Insulin (Tresiba) and Degludec Plus Aspart (Ryzodeg) for Treatment of Type 1 or 2 Diabetes

- **Key Facts:** Insulin degludec (Tresiba®) is an ultra-long-acting basal insulin analog in development for treating T1DM and T2DM in patients requiring insulin therapy. Insulin degludec/insulin aspart (Ryzodeg®) is soluble formulation of insulin degludec (70%) combined with insulin aspart (30%) (NovoLog®), a fast-acting mealtime insulin analogue. This combination is intended for patients with T1DM or T2DM. Novo Nordisk a/s (Bagsvaerd, Denmark) is developing insulin degludec and insulin degludec/insulin aspart. In September 2011, the company submitted new drug applications (NDAs) to FDA for insulin degludec and insulin degludec/insulin aspart. In December 2013, the manufacturer reported outcomes from a study involving 447 patients with T2DM treated with twice-daily insulin degludec/insulin aspart: Ryzodeg achieved the primary endpoint of noninferiority to biphasic insulin aspart 30 (mean change in HbA_{1c} from baseline) and secondary endpoint of superiority in lowering fasting plasma glucose compared with biphasic insulin aspart 30. In April 2013, Meneghini and colleagues reported outcomes from a study involving 687 patients with T2DM treated with once-daily insulin degludec compared with insulin glargine. The authors reported no statistically significant differences in overall or nocturnal hypoglycemia between the two groups; both groups had comparable results for glycemic control, hypoglycemia, and adverse events.

  In November 2012, FDA's Endocrinologic and Metabolic Drugs Advisory Committee recommended approval of this therapy for both drugs. In February 2013, the company announced that FDA issued a complete response letter regarding the NDAs, indicating that the applications could not be approved in their current form. According to the company, FDA requested additional cardiovascular data from a dedicated cardiovascular outcomes trial. A global cardiovascular outcomes trial is under way comparing insulin degludec to insulin glargine in patients with T2DM at high risk of cardiovascular events. Prespecified interim analysis of major adverse cardiovascular events is anticipated by mid-2015 and the company expects to complete the trial within 3–5 years from its October 2013 trial initiation. Insulin degludec and insulin degludec/insulin aspart have received marketing authorization from the European Commission. Although cost information is not available at this time, costs are expected to exceed available long-acting insulins. Reports in Europe have indicated that insulin degludec has cost 60% to 70% more than competitors on the European market.
- **Key Expert Comments:** Overall, experts commenting on these interventions generally agreed upon their potential to improve patient health. Experts cited adequate glycemic control, improved medication adherence, and the potential to reduce disease-related comorbidities. However, some experts expressed concerns over the potential for

cardiovascular risks. Experts anticipated moderate acceptance by patients and clinicians due to the reduced amount of required injections. However, several experts cited cost and insurance coverage to be major barriers to acceptance. One expert opined that third-party payers are likely to limit use and require preauthorization. Experts agreed that ultra-long-acting insulins have the potential to improve insulin therapy compared with available treatment options. However, some experts determined the reduced frequency of injecting ultra-long-acting insulins compared with long-acting insulins to be an incremental benefit.

- **Potential for High Impact:** Lower end of the high-impact-potential range

ITCA 650 (Exenatide Continuous Subcutaneous Delivery) for Treatment of Type 2 Diabetes

- **Key Facts:** ITCA 650 (Intarcia Therapeutics, Inc., Hayward, CA), is extended-release exenatide for injection (Bydureon™, Amylin Pharmaceuticals, a subsidiary of Bristol-Myers Squibb, New York, NY). ITCA 650 is a proprietary formulation of exenatide delivered through a proprietary delivery system consisting of a "matchstick-sized osmotic pump" that is inserted subcutaneously into the patient's arm or abdomen to purportedly deliver a slow and consistent flow of medication. Exenatide, a GLP-1 receptor agonist that has been available since 2005, is an incretin mimetic that patients inject twice daily, before meals. The delivery system is intended to be used for long-term subcutaneous delivery at a controlled rate, and ITCA 650 is reported to remain stable at body temperature for delivery up to 12 months, based on data presented thus far. The outpatient implantation procedure is performed by a physician and takes about 5 minutes. In March 2013, Intarcia began phase III trials of the ITCA 650/pump system.
- **Key Expert Comments:** Experts generally agreed on the need for effective T2DM treatments, citing patient adherence issues and the lack of efficacy of available treatments. They agreed on the potential of this intervention to reduce the burden of frequent injections and to provide consistent, effective treatment. However, several experts expressed concerns about the potential for side effects with GLP-1 receptor agonists, including pancreatitis and pancreatic cancer; although a causal link has not been established. Most experts opined that both clinicians and patients would be likely to accept this intervention, especially if they are achieving adequate glucose control with available GLP-1 receptor agonists. However, one expert commented that patients may not be willing to be implanted with the device if side effects persist during the implantation period. Experts generally agreed that the initial cost of the device would likely be offset by the long-term savings from reduced disease-related complications, if proven effective.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Metabolic (Bariatric) Surgery for Resolution of Type 2 Diabetes in Mildly Obese and Nonobese Patients

- **Key Facts:** Guidelines specify that bariatric surgery is indicated for individuals who are morbidly obese (i.e., body mass index [BMI] >40 kg/m^2) or individuals with a BMI >35 kg/m^2 and an associated comorbidity. One such qualifying comorbidity is diabetes, which is highly correlated with obesity, and outcomes showing resolution of T2DM in patients who have undergone bariatric surgery has generated interest in the potential of bariatric surgery to treat T2DM in less-obese patients (i.e., BMI <35 kg/m^2). The cost of the surgery varies depending on the choice of procedure (e.g., Roux en Y; lap banding; sleeve gastrectomy). Currently, insurers generally do not cover bariatric surgery in patients at these

BMIs. The average total cost for lap-band surgery is reportedly between $17,000 and $30,000, and the average cost for gastric bypass ranges from $20,000 to $35,000.

- **Key Expert Comments:** Experts commenting on this intervention opined that bariatric surgery has the potential to improve health outcomes in patients with T2DM, thereby addressing the unmet need. However, some experts questioned long-term efficacy and thought this intervention should be reserved as a last resort in treating patients who have T2DM. The procedure's invasiveness would likely affect limit adoption by patients and clinicians, thought the experts. However, some experts noted that patients may be willing to undergo surgery if the need for lifelong medication adherence is eliminated. Experts generally agreed that this use of the surgery has high potential to disrupt how T2DM patients with BMI <35 mg/kg^2 are managed, citing a shift from self-administered medication to inpatient surgery.
- **Potential for High Impact:** High

Diabetic Macular Edema Intervention

Fluocinolone Acetonide Implant (Iluvien) for Treatment of Diabetic Macular Edema

- **Key Facts:** According to the World Health Organization, people with diabetes who do not receive appropriate eye care have a 20% to 30% chance of developing clinically significant diabetic macular edema (DME). This condition leads to moderate or total vision loss over time. The main treatment for DME was macular focal/grid laser photocoagulation until August 2012, when FDA approved another therapy, ranibizumab injection (Lucentis®), a once-monthly eye injection. Iluvien® (Alimera Sciences, Inc., Alpharetta, GA) is a tiny tube containing 190 mcg of fluocinolone acetonide that is injected once into the back of the eye with a 25-gauge needle in a single, in-office procedure. Over 2–3 years, the tube purportedly releases a constant, low flow of medication; thus, it does not require monthly injections as does Lucentis. The exact mechanism of action is unknown, but fluocinolone acetonide is thought to work through its combined vasoconstrictive, anti-inflammatory, and antipruritic activity, which is inherent to corticosteroids such as fluocinolone. The manufacturer announced a Prescription Drug User Fee Act (PDUFA) goal date of September 26, 2014. The drug-device combination has been approved in Europe. If approved in the United States, it would compete with ranibizumab and aflibercept (Eylea®) injections; the latter is in phase III trials for treating DME. Fluocinolone acetonide's history of regulatory rejections and potential risk of increasing intraocular pressure might dissuade physicians from embracing fluocinolone acetonide implants to treat DME until a larger body of evidence becomes available.
- **Key Expert Comments:** Overall, experts commenting on this intervention opined that this intervention could offer a long-lasting, single-procedure pharmacotherapy as an alternative to laser photocoagulation or monthly injections of ranibizumab for treating DME. However, experts were unsure whether this intervention would be as effective as monthly injections of ranibizumab, because of the lack of comparative clinical trials. Experts also expressed concerns regarding potential adverse events, including cataracts and increased intraocular pressure. Experts generally agreed that this intervention has the potential to be widely accepted by patients and clinicians. However, several experts commented that the risk of adverse events could affect patient and clinician adoption, although other experts opined that patients might be willing to accept this risk if it prevents vision loss. Experts noted that the

intervention has the potential to reduce per-patient costs of treatment. However, some experts noted that cost savings could be nullified if patients need to be treated for device-related adverse events.

- **Potential for High Impact:** Lower end of the high-impact-potential range

Diabetes Mellitus Interventions

Artificial Pancreas Device Systems for Treatment of Diabetes (MiniMed 530G with Enlite Low-Glucose Suspend System)

Unmet need: Fluctuating glucose levels make diabetes management and control difficult, often requiring adjustments to insulin dosage in diabetic patients requiring insulin. Researchers estimate that two-thirds of diabetic patients do not achieve adequate glycemic control using traditional glucose meters and continuous glucose monitors (CGMs) to guide insulin treatment. This increases the risk of secondary complications, including cardiovascular disease, retinopathy, nephropathy, and neuropathy. Therefore, a medical need exists for systems that improve insulin delivery methods and glycemic control.[1-3]

The artificial pancreas device system (APDS) is intended to provide a complete system, known as a closed-loop system, to mimic pancreatic activity by combining several technologies—a glucose monitoring device, an external or implantable insulin pump, and a glucose sensor with advanced-algorithm software—to optimize diabetes management.[4]

Intervention: Fully automated APDSs are several years away from availability, but systems incorporating some of the functionality of a fully automated APDS are starting to emerge in the U.S. market. One class of technology being developed is a system that continuously monitors glucose levels and automatically adjusts insulin delivery in response to those levels.[5] One such system is the MiniMed 530G System, which integrates a low-glucose suspend (LGS) algorithm intended to reduce the severity and duration of hypoglycemic events by automatically suspending insulin administration when a person's glucose levels drop below a preset level.

An APDS consists of an external or implantable insulin pump, a system that can monitor blood glucose levels in real time, and a small computing device that uses an algorithm to determine insulin dosage delivery.[4] The computerized algorithm is designed to deliver appropriate doses of insulin from the insulin pump.[6]

In a November 2012 guidance document on APDS development,[5] the U.S. Food and Drug Administration (FDA) defined the components of APDSs as follows, stating that they are categorized as Class III devices:[7]

- Glucose monitoring devices—a CGM and blood glucose device used for calibrating the CGM (as applicable) and checking sensor performance as needed plus associated reagents/test strips
- APDS control algorithm
- Infusion pump—a fluid infusion set for the complete fluid pathway from the drug reservoir or fluid source container (e.g., bag, cassette, vial, syringe), infusion set, extension sets, filters and valves, clamps, up through the patient connection
- Components and accessories (e.g., power cord, wireless controller)

This definition includes a closed-loop system as well as first-generation systems LGS systems. For an implantable APDS, an endocrinologist administers local anesthesia and surgically implants the pump and glucose monitor subcutaneously on opposite sides of the abdomen. The insulin reservoir is placed beneath the skin and is refilled every 2–3 months via transcutaneous injection.[4] In LGS APDSs, insulin delivery automatically shuts off when blood glucose levels drop below a preset threshold indicating hypoglycemia (reactive), or the monitor uses control algorithms to predict and prevent potential hypoglycemic events (predictive).[5]

The MiniMed 530G with Enlite® sensor is the first LGS system on the market. It is intended for patients with diabetes who need exogenous insulin and wish to use a pump with a CGM system. The system is considered a first-generation APDS incorporating a reactive LGS algorithm. The system uses threshold suspend automation to automatically stop insulin delivery (for up to 2 hours)

when sensor glucose values reach a preset level and when the patient does not respond to the threshold suspend alarm.[8]

The MiniMed 530G system consists of the following:[9]

- An insulin pump with CGM
- The new Enlite continuous glucose sensor (with Enlite Serter)
- The new Contour® Next Link wireless blood glucose meter (Bayer Diabetes Care, Tarrytown, NY)

Clinicians and patients can use Medtronic's CareLink® Pro Therapy Software with the MiniMed 530G to monitor blood glucose levels and manage diabetes care.[9]

Medtronic reports that its Enlite sensor can be worn for 6 days, is 69% smaller than the company's previous-generation sensor, and offers a 31% improvement in overall accuracy compared with the previous model. According to the company, "the new Enlite Serter provides a simpler sensor insertion process with a hidden-introducer needle."[8]

The MiniMed 530G system uses the same calibration algorithm and threshold suspend software used in Medtronic's Veo™ insulin pump, which was developed earlier and is sold in Europe.[10] Like the MiniMed 530 G system, the LGS feature of the Veo insulin pump system was designed to reduce the severity and duration of hypoglycemia. Patients may use the pump with or without CGM sensors, and CGM-augmented Veo pump users may turn the LGS feature on or off.[11]

Clinical trials: Many APDS proof-of-concept trials are ongoing in the United States and internationally. Much of the research is supported by the Juvenile Diabetes Research Foundation (JDRF). In June 2014, Russell and colleagues reported outcomes from 5-day, random-order, crossover studies assessing the safety and efficacy of a "bionic" pancreas system in 20 adults and 32 adolescents with type 1 diabetes (T1DM). The authors reported the following results:[12]

> Among the adults, the mean plasma glucose level over the 5-day bionic-pancreas period was 138 mg per deciliter (7.7 mmol per liter), and the mean percentage of time with a low glucose level (<70 mg per deciliter [3.9 mmol per liter]) was 4.8%. After 1 day of automatic adaptation by the bionic pancreas, the mean (±SD) glucose level on continuous monitoring was lower than the mean level during the control period (133±13 vs. 159±30 mg per deciliter [7.4±0.7 vs. 8.8±1.7 mmol per liter], P<0.001) and the percentage of time with a low glucose reading was lower (4.1% vs. 7.3%, P=0.01). Among the adolescents, the mean plasma glucose level was also lower during the bionic-pancreas period than during the control period (138±18 vs. 157±27 mg per deciliter [7.7±1.0 vs. 8.7±1.5 mmol per liter], P=0.004), but the percentage of time with a low plasma glucose reading was similar during the two periods (6.1% and 7.6%, respectively; P=0.23). The mean frequency of interventions for hypoglycemia among the adolescents was lower during the bionic-pancreas period than during the control period (one per 1.6 days vs. one per 0.8 days, P<0.001).

In September 2013, Ly and colleagues reported outcomes from a study assessing the safety and efficacy of an LGS system in 95 patients with T1DM. The authors reported the following results:[13]

> Of the 95 patients randomized, 49 were assigned to the standard-pump (pump-only) therapy and 46 to the low-glucose suspension group. The mean (SD) age was 18.6 (11.8) years; duration of diabetes, 11.0 (8.9) years; and duration of pump therapy, 4.1 (3.4) years. The baseline rate of severe and moderate hypoglycemic events in the pump-only group was 20.7 vs 129.6 events per 100 patient months in the low-glucose suspension group. After 6 months of treatment, the event rates decreased from 28 to 16 in the pump-only group vs 175 to 35 in the low-glucose suspension

> group. The adjusted incidence rate per 100 patient-months was 34.2 (95% CI [confidence interval], 22.0-53.3) for the pump-only group vs 9.5 (95% CI, 5.2-17.4) for the low-glucose suspension group. The incidence rate ratio was 3.6 (95% CI, 1.7-7.5; P <.001). There was no change in glycated hemoglobin in either group: mean, 7.4 (95% CI, 7.2-7.6) to 7.4 (95% CI, 7.2-7.7) in the pump-only group vs mean, 7.6 (95%, CI, 7.4-7.9) to 7.5 (95% CI, 7.3-7.7) in the low-glucose suspension group. Counterregulatory hormone responses to hypoglycemia were not changed. There were no episodes of diabetic ketoacidosis or hyperglycemia with ketosis.

In July 2013, Bergenstal and colleagues published results from a pivotal, in-home study assessing the safety and efficacy of a LGS APDS in 247 patients with T1DM. The authors reported the following results:[14]

> This multicenter, open-label, randomized, controlled trial showed that use of the threshold-suspend feature in sensor-augmented insulin-pump therapy significantly reduced the AUC for rigorously defined nocturnal hypoglycemic events (a proxy for the severity and duration of such events), the weekly rate of nighttime hypoglycemic events, and the percentage of nocturnal time spent with sensor glucose values in the hypoglycemic range. In addition, these reductions in measures of hypoglycemia with the threshold-suspend feature were observed for the full 24-hour period. Lower exposure to hypoglycemia was consistent in subgroups of patients stratified according to age, duration of diabetes, and glycated hemoglobin level at randomization and was achieved without significant changes in glycated hemoglobin levels, severe hypoglycemic events, ketosis, or diabetic ketoacidosis. The finding that there were no significant between-group differences in the number of study visits, insulin use, sensor wear and calibrations, or number of blood glucose determinations suggests that the reduction in hypoglycemia was due to the threshold-suspend feature itself.

In June 2013, the manufacturer announced results from the ASPIRE in-home pivotal trial, which evaluated safety and efficacy of APDSs used in a home setting. The ASPIRE study reportedly met safety and efficacy endpoints and provided clinical validation for threshold suspend systems.[15]

In February 2013, Phillip and colleagues published results from a multicenter, multinational, randomized, crossover trial assessing the safety and efficacy of an APDS for controlling nocturnal glucose levels in 56 patients with T1DM. In two consecutive, overnight sessions, patients were randomly assigned to receive treatment with an APDS the first night and a sensor-augmented insulin pump (control) the second night or vice versa. The authors reported the following results:[16]

> On nights when the artificial pancreas was used, versus nights when the sensor augmented insulin pump was used, there were significantly fewer episodes of nighttime glucose levels below 63 mg per deciliter (7 vs. 22) and significantly shorter periods when glucose levels were below 60 mg per deciliter (P = 0.003 and P = 0.02, respectively, after adjustment for multiplicity). Median values for the individual mean overnight glucose levels were 126.4 mg per deciliter (interquartile range, 115.7 to 139.1 [7.0 mmol per liter; interquartile range, 6.4 to 7.7]) with the artificial pancreas and 140.4 mg per deciliter (interquartile range, 105.7 to 167.4 [7.8 mmol per liter; interquartile range, 5.9 to 9.3]) with the sensor-augmented pump. No serious adverse events were reported.

Manufacturer and regulatory status: The separate components that comprise an APDS have had marketing approval for some time.[6] FDA has issued a guidance document for the systems intended to facilitate the clinical development of a fully CLS.[17,18] In November 2012, FDA published guidelines, "The Content of Investigational Device Exemption (IDE) and Premarket

Approval (PMA) Applications for Artificial Pancreas Device Systems," to inform the sponsors of APDS IDE studies on how to support a PMA for "single patient use in the home environment."[7] In August 2013, FDA finalized the guidance and added it to resources about APDS research and development on its Web site.[19]

In June 2012, Medtronic submitted to FDA the final component of a modular PMA submission for the MiniMed 530G, supported in part by the ASPIRE in-clinic trial results.[20] Medtronic had initially promoted CGM integration by developing the MiniMed Paradigm Veo and had received FDA approval in late 2011 to begin the ASPIRE trial to evaluate a LGS APDS in the United States.[6,21] The ASPIRE clinical trial was designed to evaluate the safety and efficacy of the systems in a home setting.[21]

According to the company's submission to FDA, "A similar insulin pump system containing the threshold suspend tool received a CE [Conformité Européene] mark under the name, Paradigm Real Time Veo System, and was commercialized in the European Economic Community in May 2010."[10] The Summary of Safety and Effectiveness Data for the MiniMed 530G states the following:[10]

> The effectiveness of the Threshold Suspend tool in correctly suspending insulin delivery at the set threshold was examined using the Sof-Sensor and the Medtronic Veo insulin pump. Though this system is not identical to the 530G system, this data can be extrapolated to support the safety and effectiveness of the 530G system for the following reasons. The software for the Threshold Suspend tool is the same for the Veo pump and the 530G System. Though the Medtronic Sof-Sensor and the Enlite sensor are not identical, they operate using similar principles and fundamental scientific technology.

FDA approved the MiniMed 530G with Enlite system for marketing in September 2013. The indication is "for use by people with diabetes ages 16 and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin."[8] The MiniMed 530G is the first system to be approved under FDA's new product classification, "OZO: Artificial Pancreas Device System, Threshold Suspend."

In accordance with FDA approval, Medtronic will conduct a postapproval study that will include children aged 2 years or older. The company's press release further stated: "As a condition of approval, in addition to the post-approval study, Medtronic will engage in direct patient follow up and will make certain manufacturing accommodations. These commitments are consistent with the product approval by the FDA and an accompanying warning letter issued to Medtronic on Sept. 19, 2013. Medtronic has already addressed many of the observations noted in the warning letter and is committed to resolving the remaining observations as quickly as possible and in accordance with the product approval requirements."[8]

At least three companies are pursuing APDSs.[22] Medtronic and another company, Tandem Diabetes Care, Inc. (San Diego, CA), have formed a partnership with JDRF to advance technologies toward achieving a fully automated monitor/pump combination.[23] Animas Corp., a unit of Johnson & Johnson (New Brunswick, NJ), and DexCom, Inc. (San Diego, CA), have collaborated to develop the Animas Vibe combined insulin pump and CGM, which received the CE mark in June 2011, allowing marketing in Europe. It has also been released in the United Kingdom.[21] In April 2013, Animas submitted a PMA application to FDA for the device, and the company is working through a second feasibility study.[22,24] The next generation of Medtronic APDS is the predictive type that suspends insulin delivery when the system predicts hypoglycemia in the patient.[25]

Diffusion and cost: The most appropriate patients are considered to be those with T1DM who frequently experience hypoglycemia, are highly motivated to achieve control, and are able to use an insulin pump.[26,27] Among suitable candidates, patients who have trouble maintaining normal

nocturnal glycemia are especially expected to want to adopt use of an APDS.[28] Diffusion may take place at centers of excellence because of the level of expertise and comprehensive training required for using and monitoring device function.[29] However, if the APDS effectively slows disease progression, the device might become more widely available as the most desirable method for diabetes management in patients who require daily insulin.[3,30] Diffusion of the newly approved Medtronic MiniMed 530G began in late 2013. Medtronic introduced a program to aid adoption called the Path2System Program.[31] This enables patients who already have an "existing, in-warranty Paradigm® Revel™ Insulin Pump and Continuous Glucose Monitoring" to order MiniMed 530G with Enlite for $399 plus the cost of the Enlite starter kit. The company advises that patients' out-of-pocket costs for CGM vary according to their health plan coverage. The Path2System includes the pump; Enlite training packet; data transmitter, charger, and test plug; and the Enlite Starter Kit. Medtronic states that patients should expect a wait of 90 days after applying for the program because of high demand. According to a September 2013 report, the anticipated retail price for MiniMed 530G was $7,350 for those ineligible for the Path2System Program; insured patients reportedly typically pay $500 to $1,200 out of pocket, depending on their insurance co-payments.[32]

Although a true APDS may raise the cost over that of standard CGM and insulin pumps, a study funded by JDRF projected the technology could reduce diabetes-related expenses by slowing disease progression.[3,30,33] Total estimated costs of diagnosed diabetes in the United States are $245 billion, and an additional $69 billion is attributed to reduced productivity.[33]

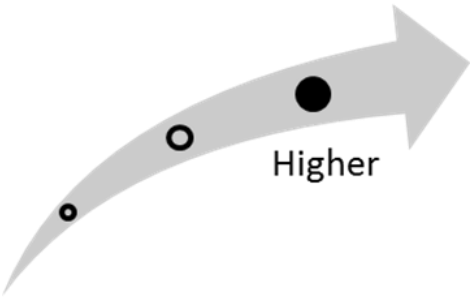
The U.S. Centers for Medicare & Medicaid Services (CMS) does not have a coverage policy for use of this technology. In June 2014, we searched 13 representative third-party payers to identify whether they have policies that mention the MiniMed 530G device. We found five policies indicating that the following payers provide coverage: Aetna,[34] Blue Cross Blue Shield (BCBS) of Alabama,[35] CIGNA,[36] Excellus BCBS,[37] and Humana.[38] These payers typically provide coverage when certain eligibility criteria are met, including the labeled indication criteria. Several other payers, such as BCBS Massachusetts, BCBS North Carolina, HealthNet, and United HealthCare, have policies stating they do not provide coverage. They consider the device to be investigational at this time. Still other payers have no policy mentioning the system.

As the first system approved under FDA's new "Artificial Pancreas Device System, Threshold Suspend" product classification, the MiniMed 530G system might warrant a new CMS reimbursement category. Medtronic has reportedly applied for a new CMS code for the system, which is currently covered by existing CMS codes for insulin pumps and CGM.[39]

Clinical Pathway at Point of This Intervention

Upon receiving a diagnosis of diabetes, patients undergo medical evaluation to classify the disease type, detect any complications, review glycemic control challenges, and establish a treatment plan (depending on diabetes type and other medical factors). Part of this plan is establishing target glycated hemoglobin (HbA_{1c}) goals. HbA_{1c} is a measure of the average amount of glucose in a patient's blood over a 3- or 4-month period based on a single blood draw. Patients with T1DM require insulin therapy. For type 2 diabetes mellitus (T2DM), one or more self-administered oral antidiabetes agents taken alone or in combination are generally tried as first-line therapy. Some patients with T2DM also need insulin therapy.[40] Clinicians encourage patients to achieve an HbA_{1c} level of about 7% or slightly lower, depending on the patient. This value has been shown to reduce some secondary complications associated with T1DM and T2DM. Patients and their diabetes care teams work to adjust insulin dosages using feedback from a blood glucose monitor.[6]

Figure 1. Overall high-impact potential: artificial pancreas device system (MiniMed 350G Low Glucose Suspend System) for treatment of diabetes requiring exogenous insulin



Overall, experts commenting on this intervention opined that it has the potential to improve patient health outcomes, especially in patients with hypoglycemia unawareness, by reducing hypoglycemic episodes. However, experts commented that the device's potential to improve patient health is limited by its inability to address hyperglycemic episodes. Most experts commented that this intervention represents an important step towards a true APDS. Experts generally agreed upon the potential for widespread clinician and patient acceptance. However, some experts cited cost, insurance coverage, and device training to be potential barriers to acceptance. Most experts agreed that this intervention is not likely to affect health disparities. However, some experts commented that patients without health insurance may not be able to afford the out-of-pocket costs of the device. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on the MiniMed 530G with Enlite.[41-46] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A significant need exists for interventions that continuously monitor blood glucose and automatically adjust insulin delivery in patients with diabetes who require exogenous insulin, noted experts. They commented that this intervention has the potential to improve patient health outcomes by reducing hypoglycemic episodes. One clinical expert deemed the intervention to be advantageous because it can accurately predict hypoglycemia. The expert commented, "These features will benefit the treatment of type 1 and type 2 diabetes, as well as prevent morbidity in patients with hypoglycemia unawareness, a potentially deadly consequence of repeated hypoglycemic episodes associated with insulin therapy."[46] Some experts expressed concerns over the intervention's inability to respond to hyperglycemic episodes. One expert representing a research perspective opined, "The device under question will potentially minimize hypoglycemic events, which in and of itself is highly beneficial. When we have a system that can minimize hyperglycemic events, which are key factors for severe diabetic complications, then we will have made a huge step forward...."[45]

Acceptance and adoption: Experts noted that both patients and physicians would widely accept this intervention because of the benefits of increased glycemic control. One expert representing a research perspective opined, "I suspect there will be wide acceptance of this technology based on its clinical benefits and patient's ease of use post the learning period. This wide acceptance is predicated on the confidence of the clinicians regarding the accuracy of the technology to prevent hypoglycemia and respective complications."[42] Experts commenting on this intervention listed training and reimbursement to be potential barriers to acceptance for patients.

However, one expert representing a research perspective opined that patients familiar with insulin pump use would easily grasp the concepts of device use.[44]

Health care delivery infrastructure and patient management: Most experts listed the health care professional training to be the largest potential disruption to health care delivery infrastructure. One expert representing a clinical perspective opined that sophisticated training would be required that would not likely be provided at a primary care clinic.[46] However, one expert representing a research perspective opined that this intervention would not likely affect centers familiar with insulin pump therapy. The expert commented, "Facilities that currently offer pump therapy programs already have in place multidisciplinary teams that would care for these patients… patients experienced in pump use would readily grasp concepts of device use."[44]

Most experts generally agreed that this intervention has a minimal potential to disrupt patient health management after the initial patient and clinician training phase is completed. One expert representing a research perspective anticipated a reduction in other medical services, including emergency room visits, intensive care services, and physician services.[42]

Health disparities: Most experts agreed that this intervention is not likely to impact health disparities. Some experts commented that patients without health insurance may not be able to afford the out of pocket costs of the device. However, one expert representing a research perspective opined, "Currently, pump users are highly educated, motivated patients with financial means to afford out-of-pocket expenses related to pump use."[44]

Degludec Ultra-Long-Acting Insulin (Tresiba) and Degludec Plus Aspart (Ryzodeg) for Treatment of Type 1 or 2 Diabetes

Unmet need: About two-thirds of patients requiring insulin therapy do not achieve adequate glycemic control, increasing their risk of secondary complications (i.e., cardiovascular disease, retinopathy, nephropathy, neuropathy). Adherence to available insulin delivery methods and self-monitoring of blood glucose are two of the factors affecting adequate management. Despite available insulin formulations, pumps, and oral antidiabetic medications, optimal blood glucose control remains a challenge for many patients who require insulin therapy. Therefore, a need exists for improved insulin options to improve glycemic control. Pharmacotherapy designed to improve the effectiveness and duration of insulin is warranted. Insulin degludec purportedly provides steady insulin coverage significantly longer than other long-acting basal insulin products.

Intervention: Insulin degludec (Tresiba®) is an ultra-long-acting basal insulin analog in development for treating T1DM and T2DM in patients requiring insulin therapy. Insulin degludec reportedly offers a flat and predictable action profile by forming soluble multihexamer assemblies, providing longer than 24-hour coverage with once-daily subcutaneous injection.[47,48] Upon subcutaneous injection, insulin degludec forms soluble multihexamers (polypeptides), resulting in a "depot" from which it is purportedly continuously absorbed into the circulation over 24–40 hours.[49] Thus, insulin degludec has potential to reduce the number of injections a patient requires each week. Insulin degludec has been developed in formulations of 100 units (U)/mL (600 nmol/mL) and 200 U/mL (1,200 nmol/mL).[50]

Insulin degludec/insulin aspart (Ryzodeg®) is soluble formulation of insulin degludec (70%) combined with insulin aspart (30%) (NovoLog®), a fast-acting mealtime insulin analogue.[51,52] This combination is indicated for patients in whom T1DM or T2DM has been diagnosed.[53] In clinical trials, insulin degludec was administered subcutaneously, in combination with insulin aspart at a dose of 100 U/mL.[50,54] Both insulin degludec and insulin degludec/insulin aspart will reportedly be supplied in prefilled, disposable pens with automatic injection technology.[55]

Clinical Trials: In December 2013, the manufacturer reported outcomes from a study involving 447 patients with T2DM treated with twice daily insulin degludec/insulin aspart:[56]

> Ryzodeg achieved the primary endpoint of non-inferiority to biphasic insulin aspart 30 for mean change in HbA_{1c} from baseline (estimated treatment difference [ETD] –0.03% points, 95% CI –0.18; 0.13). Ryzodeg® achieved the secondary endpoint of superiority in lowering FPG [fasting plasma glucose] compared with biphasic insulin aspart 30 (ETD –1.14 mmol/L, 95% CI – 1.53; –0.76, p<0.001). Final mean daily insulin dose was 11% lower for Ryzodeg® compared with biphasic insulin aspart 30 (1.08 U/kg versus 1.20 U/kg; estimated rate ratio [RR] 0.89, 95% CI 0.83; 0.96, p=0.002).

In April 2013, Meneghini and colleagues reported outcomes from a study involving 687 patients with T2DM treated with insulin degludec (IDeg) administered at intervals of 8–40 hours (OD Flex); once-daily IDeg at the evening meal (OD), or insulin glargine at the same time each day (IGlar OD). The authors reported the following results:[57]

> After 26 weeks, IDeg OD Flex, IDeg OD, and IGlar OD improved HbA(1c) by 1.28, 1.07, and 1.26% points, respectively (estimated treatment difference [IDeg OD Flex - IGlar OD]: 0.04% points [-0.12 to 0.20], confirming noninferiority). No statistically significant differences in overall or nocturnal hypoglycemia were found between IDeg OD Flex and IGlar OD. Comparable glycemic control and rates of

hypoglycemia were seen with IDeg OD Flex and IDeg OD. Adverse event profiles were similar across groups.

In March 2013, Mathieu and colleagues reported outcomes from a study involving 493 patients with T1DM treated with once-daily insulin degludec compared with insulin glargine. The authors reported the following results:[58]

> After 26 treatment weeks, mean glycosylated hemoglobin was reduced with IDeg Forced- Flex (-0.40%), IDeg (0.41%), and IGlar (-0.58%). IDeg Forced-Flex noninferiority was achieved. Fasting plasma glucose reductions were similar with IDeg Forced-Flex and IGlar but greater with IDeg (-2.54 mmol/L) than IDeg Forced-Flex (-1.28 mmol/L) (P = .021). At week 52, IDeg Free-Flex subjects had similar glycosylated hemoglobin but greater fasting plasma glucose reductions than IGlar subjects (-1.07 mmol/L) (P = .005). Confirmed hypoglycemia rates (plasma glucose <3.1 mmol/L or severe hypoglycemia) were similar at weeks 26 and 52. Nocturnal confirmed hypoglycemia was lower with IDeg Forced-Flex vs IDeg (37%; P = .003) and IGlar (40%; P = .001) at week 26 and 25% lower with IDeg Free-Flex vs IGlar (P = .026) at week 52.

Manufacturer and regulatory status: Novo Nordisk a/s (Bagsvaerd, Denmark) is developing insulin degludec and insulin degludec/insulin aspart for treating T1DM and T2DM. In September 2011, the company submitted new drug applications (NDAs) to FDA for both insulin degludec and insulin degludec/insulin aspart.[59] In November 2012, FDA's Endocrinologic and Metabolic Drugs Advisory Committee recommended approval of this therapy for both drugs.[53] In February 2013, the company announced that FDA issued a complete response letter regarding the NDAs for insulin degludec and insulin degludec/insulin aspart, indicating that the applications could not be approved in their current form. According to the company, FDA requested additional cardiovascular data from a dedicated cardiovascular outcomes trial.[60] A global cardiovascular outcomes trial is under way comparing insulin degludec to insulin glargine in patients with T2DM at high risk of cardiovascular events. Prespecified interim analysis of major adverse cardiovascular events is anticipated by mid-2015, and the company expects to complete the trial within 3–5 years from its October 2013 trial initiation.[61] Insulin degludec and insulin degludec/insulin aspart have received marketing authorization from the European Commission.[62] FDA approved insulin aspart in June 2000.[63]

Diffusion and costs: Although U.S. cost information is not available at this time, costs are expected to exceed available long-acting insulins. Reports from Europe have indicated that insulin degludec costs 60% to 70% more than competitors on the European market.[64]

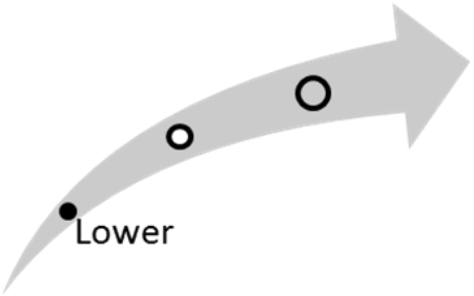
Several long-acting or basal insulin formulations available in the United States, including insulin glargine (Lantus®) and insulin detemir (Levemir®), might compete with degludec, although degludec is intended to last much longer.[65,66] Glargine and detemir provide a sustained, uniform plasma concentration that lasts 11–26 hours. Long-acting insulins are used to meet the low steady-state (i.e., basal) insulin supply needed for continuous metabolic functions. Both formulations are widely used in multicomponent insulin regimens that use once- or twice-daily injections of long-acting insulin to provide basal coverage supplemented by injections of short-acting insulin formulations at mealtimes.

Clinical Pathway at Point of This Intervention

Upon diagnosis, patients undergo medical evaluation to classify the disease type, detect any complications, review glycemic control challenges, and establish a treatment plan (depending on diabetes type and other medical factors). Part of this plan is establishing target HbA_{1c} goals. HbA_{1c}

is a measure of the average amount of glucose in a patient's blood over a 3- or 4-month period based on a single blood draw. Patients with T1DM require insulin therapy. For T2DM, one or more self-administered oral antidiabetes agents taken alone or in combination are generally tried as first-line therapy. Some patients with T2DM also need insulin therapy.[40] Clinicians encourage patients to achieve an HbA_{1c} level of about 7% or slightly lower, depending on the patient. This value has been shown to reduce some secondary complications associated with T1DM and T2DM. Patients and their diabetes care teams work to adjust patient insulin dosages using feedback from a blood glucose monitor.[6]

Figure 2. Overall high-impact potential: degludec ultra-long-acting insulin (Tresiba) and degludec plus aspart (Ryzodeg) for treatment of type 1 or 2 diabetes



Overall, experts commenting on these interventions generally agreed on their potential to improve glycemic control, medication adherence, and reduce disease-related comorbidities. Some experts expressed concerns about the potential for cardiovascular risks. Experts anticipated acceptance by patients and clinicians because of the drugs' potential to improve medication adherence. However, several experts cited cost and insurance coverage to be possible barriers to acceptance. One expert opined that third-party payers are likely to limit use and require preauthorization. Experts agreed that ultra-long-acting insulins have the potential to improve insulin therapy compared to available treatment options. However, some experts determined the reduced frequency of injecting ultra-long-acting insulins to long-acting insulins to be an incremental benefit. Based on this input, our overall assessment is that this intervention is in the lower high-impact-potential range.

Results and Discussion

Six experts, with clinical, research, health devices, health systems, and health administration backgrounds, provided perspectives on this intervention.[67-72] One of these experts declared a potential conflict of interest (COI) because the expert is a consultant for the manufacturer.[68] This potential COI is balanced by the perspectives of other experts who reported having no COIs. We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Most experts commenting on this intervention agreed on the need for treatment that could help patients achieve desired glucose control and reduce disease-related comorbidities. One expert representing a clinical perspective opined, "Most patients requiring insulin therapy for diabetes do not achieve adequate glucose control, increasing their risk of cardiovascular disease, retinopathy, nephropathy and neuropathy. Poor glycemic control is partly due to inadequate insulin formulations and poor self-monitoring of blood glucose."[67] However, several experts noted the availability of long-acting insulins that can be administered daily. One expert representing a health devices perspective opined, "This drug does not introduce a new type

of treatment or class of drug, so I think it has limited ability to impact the need for effective diabetes treatments."[72]

Most experts agreed on the potential of this intervention to improve patient health outcomes, citing enhanced prandial and fasting glycemic control, and stable basal insulin. Some experts commented that the reduced injection frequency could improve patient adherence to therapy. Several experts commenting on this intervention expressed concerns regarding potential adverse events and cardiovascular safety. One expert representing a clinical perspective opined, "Severe hypoglycemia events are few in patients treated with ultra-long-acting insulin, but this needs to be monitored in the long term, because hypoglycemia may increase the risk of adverse cardiovascular events and death. Moreover, the potential consequences of long acting insulin therapy on tumor growth needs to be considered."[67]

Acceptance and adoption: This intervention has moderate potential for acceptance by patients and clinicians, experts thought. They opined that clinicians would likely adopt ultra-long-acting insulins if it is proved to be safe and effective and that patients would be likely to accept this intervention for its convenience. Most experts listed cost to be the largest potential barrier to acceptance. One expert representing a research perspective commented that cost would likely prohibit patients with middle to low incomes from obtaining this medication.[73]

Health care delivery infrastructure and patient management: Major disruption to health care delivery infrastructure would not be seen, the experts thought. Most experts listed the similarities of care delivery of ultra-long-acting insulins to available long-acting insulins.

Experts generally agreed that this intervention has minimal potential to change patient management. Some experts noted the potential for this intervention to reduce emergency department and physician office visits, if the drug is proved safe and effective.

Health disparities: Several experts thought the impact on health disparities would be minimal. One expert representing a research perspective listed increased costs compared with available therapy and access to diabetes management services as potential factors affecting health disparities.[69]

ITCA 650 (Exenatide Continuous Subcutaneous Delivery) for Treatment of Type 2 Diabetes

Unmet need: Despite the availability of oral antidiabetes drugs, many patients with T2DM do not meet treatment goals and require additional therapy with one of two types of injected antidiabetic agents: subcutaneous insulin or a glucagon-like peptide 1 (GLP-1) receptor agonist, also called an incretin mimetic.[74] Incretin mimetics have become standard treatments to improve glycemic control.[40] However, the GLP-1 receptor agonists approved by FDA—exenatide (Byetta®), liraglutide (Victoza®), and exenatide long-acting release (Bydureon™)—require twice daily, once daily, or once weekly dosing, respectively, by subcutaneous injection.[75,76] More convenient dosing could potentially improve adherence to treatment recommendations and patient outcomes. ITCA 650 is in development and involves use of the GLP-1 receptor agonist exenatide, delivered through an implantable device providing a steady dose for up to 12 months.[77]

Intervention: ITCA 650 is a matchstick-sized, implantable device that is intended to deliver a steady dose of an incretin mimetic, exenatide, using a proprietary delivery system (Duros® technology). Exenatide, which has been available since 2005, is an incretin mimetic that patients inject twice daily, before meals. The new Duros delivery system is intended to deliver the drug subcutaneously, at a controlled rate over the long term. It has been used commercially since 2000 in a leuprolide acetate implant (Viadur®) for treating advanced prostate cancer.[78] The system is a miniature osmotic pump that essentially functions as a syringe.[78] Within a tubular titanium shell, the system contains a drug reservoir and an osmotic agent separated by a piston. Adjacent to the osmotic agent is a semipermeable membrane. The osmotic agent steadily draws water from the body across the membrane, which exerts pressure on the piston, forcing a steady flow of drug out of a small pore or diffusion moderator on the opposite side of the pump. Studies have demonstrated that the formulation of exenatide used in ITCA 650 is stable within the Duros pump for at least 1 year at body temperature, potentially allowing once-yearly system implantation.[79]

A physician or physician assistant inserts ITCA 650 into the patient's arm or abdomen during an outpatient procedure that takes about 5–10 minutes.[77] Clinicians can remove or replace the device in a similarly short procedure. The version of ITCA 650 that will be used in phase III clinical trials is intended to deliver a dose of 60 mcg of exenatide per day.[80]

Clinical trials: The safety and efficacy of the ITCA 650 pump system compared with twice-daily exenatide injections (Ex-BID) was evaluated in a two-stage, phase II trial in patients with T2DM inadequately controlled with metformin.[81] Stage I (n=155) evaluated patient outcomes after 12 weeks of treatment with 20 or 40 mcg/day of ITCA 650 or Ex-BID. Stage II (n=131) randomly reassigned patients to receive 20, 40, 60, or 80 mcg/day of ITCA 650 for an additional 12 weeks. Henry and colleagues published the following results in May 2013:[81]

> HbA1c was significantly lower in all groups after 12 and 24 weeks. Stage I: mean change in HbA_{1c} from a mean baseline of 7.9-8.0% was -0.98, -0.95, and -0.72% for the 20 and 40 μg/day ITCA 650 and Ex-BID groups, respectively, with 63, 65, and 50% of subjects achieving HbA_{1c} levels ≤7% ($P < 0.05$). Stage II: significant ($P < 0.05$) reductions in HbA_{1c} (~1.4% from baseline) were achieved with 60 and 80 μg/day ITCA 650, and 86 and 78% of subjects achieved HbA_{1c} ≤7% at 24 weeks; respectively. Weight was reduced by 2.8-3.7 kg ($P < 0.05$) at 24 weeks in all except the 20→20 μg/day group. ITCA 650 was well-tolerated; nausea was lower and transient with 20 μg/day relative to Ex-BID; and 60 μg/day had the best profile of tolerability and $HbA1_c$ lowering.

In March 2013, ITCA 650's developer announced enrolling the first patients in its phase III FREEDOM clinical program, which is expected to include more than 4,000 patients at 500 clinical trial sites in more than 30 countries. The studies will include a broad range of patients whose diabetes is uncontrolled by oral antidiabetes medications including metformin and metformin-based combinations.[82]

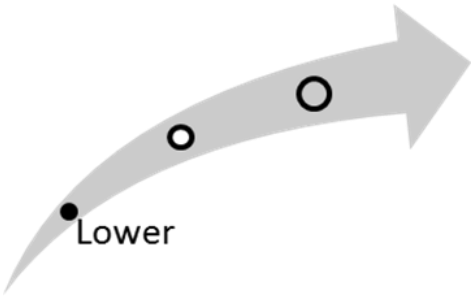
Manufacturer and regulatory status: Intarcia Therapeutics, Inc. (Hayward, CA), is developing the ITCA 650 system for continuous subcutaneous delivery of exenatide. Two phase II clinical trials have been completed.[83] Intarcia has announced enrollment in its phase III FREEDOM trial to evaluate ITCA 650 in patients with T2DM.[84] The trial is being conducted in collaboration with Quintiles, Inc. (Durham, NC), a global clinical research organization.[84]

Diffusion: ITCA 650 is most likely to compete with injected exenatide (administered twice daily) and liraglutide (administered once daily).[75,76] The cost for ITCA 650 has not been determined, but it will likely be priced at a slight premium to existing injectable exenatide formulations because of its novelty and convenience.[85] Although ITCA 650 use would add to the up-front cost of therapy, it could potentially save costs if it improves patient adherence to prescribed treatment, slows disease progression and development of secondary complications, and eliminates the attendant health services needed to treat those complications.

Clinical Pathway at Point of This Intervention

T2DM typically occurs later in life, although incidence in a younger population has been growing as a result of the obesity epidemic. Initial treatment includes dietary modification, exercise, and self-monitoring of blood glucose. First-line drug therapies include biguanides, sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and dipeptidyl peptidase-4 inhibitors. Some patients require combination drug therapy of agents with different mechanisms of action for additive therapeutic effects and better glycemic control. Despite the availability of oral antidiabetes drugs, many patients do not achieve treatment goals and require additional therapy with an injected antidiabetes agent: subcutaneous insulin or a GLP-1 agonist.[74]

Figure 3. Overall high-impact potential: ITCA 650 (exenatide continuous subcutaneous delivery) for treatment of type 2 diabetes



Overall, experts commenting on this intervention agreed on the need for effective T2DM treatments, citing patient compliance issues and the lack of efficacy of available treatments. Experts commented that this intervention has the potential to improve patient health by reducing the burden of frequent injections. Several experts expressed concerns over the potential for side effects with GLP-1 receptor agonists, including pancreatitis and pancreatic cancer; although a causal link has not been established. Experts agreed upon the potential for widespread acceptance by both clinicians and patients. Patients would likely accept this intervention, especially if they are achieving adequate glucose control with available GLP-1 receptor agonists. However, one expert commented that patients may not be willing to be implanted with the device if side effects persist

during the implantation period. Experts generally agreed that the initial cost of the device would likely be offset by the long-term savings from reduced disease-related complications, if ITCA 650 is proved effective. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on ITCA 650 (subcutaneous exenatide).[86-91] We have organized the following discussion of expert comments by the parameters on which experts commented.

Unmet need and health outcomes: ITCA 650's subcutaneous delivery could improve patient adherence to therapy and therefore significantly address an unmet need, the experts commenting on this intervention generally agreed. One clinical expert stated, "Diabetes is a significant disease state where compliance with treatment has a clear impact on overall control and treatment. Although there are other GLP-1 receptor agonists available there is no other long-term depot type/or other long term delivery system available on the market. It would likely result in the highest degree of consistent treatment."[87]

This intervention has the potential to improve patient health outcomes, most experts agreed, citing the intervention's long-term glycemic control and the potential to reduce disease-related comorbidities. One expert representing a research perspective commented, "The medication, exenatide, is already an established therapy in the management of type 2 diabetes. The mode of delivery, an implanted pump, is an established therapy for other drugs or other treatments. The benefit of the pump is that it can assist patients in more consistent and accurate dosing of exenatide, and will increase patient compliance."[88] However, some experts expressed concerns about potential adverse events. One expert representing a clinical perspective opined, "As with other GLP1 drugs, there are concerns about pancreatitis, pancreatic cancer and thyroid cancer which need to be monitored over time."[86]

Acceptance and adoption: Experts agreed on the potential for widespread acceptance by both clinicians and patients. Patients would likely accept this intervention, especially if they are achieving adequate glucose control with available GLP-1 receptor agonists, the experts thought. One expert representing a research perspective opined, "Patients are very likely to accept this course of treatment. It requires only a short in-office procedure for insertion and removal. Side effects are minimal. Unlike other treatments for T2DM, management of therapy with the ITCA 650 is controlled by the device and requires no input by the patient and no ongoing often painful procedures for administration."[90] Alternatively, one health systems expert commented that patients may not be willing to undergo device implantation due to concerns regarding continued adverse events.[89]

Health care delivery infrastructure and patient management: Experts commenting on this intervention agreed on a minimal disruption to health care delivery infrastructure, citing the straightforward method of device implantation.

Overall, patient management would likely experience a minimal disruption, the experts commented. According to one research expert, the addition of this intervention is not likely to cause a major disruption because comprehensive nature of diabetes management.[88]

Health disparities: This intervention would have a minimal potential impact on health disparities, thought experts. Some listed cost and limited access to care as potential factors that could increase disparities. However, one research expert opined that this treatment has the potential to improve health disparities, "Patients with less access to care (socioeconomic, geographically

limited) may be the best targets for this type of long delivery system as they are likely to be less amenable to the lifestyle of daily or weekly injectables."[91]

Metabolic (Bariatric) Surgery for Resolution of Type 2 Diabetes in Mildly Obese and Nonobese Patients

Unmet need: Two-thirds of diabetes patients, especially those requiring insulin therapy, do not achieve adequate glycemic control. This increases their risk of secondary complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy. Metabolic surgery has been proposed as a therapy for inducing T2DM remission in patients who have been unable to achieve adequate control with first- or second-line therapy and whose body mass index (BMI) is lower than that typically required for patient eligibility for bariatric surgery.

Intervention: Metabolic surgery has become a therapy used to induce T2DM remission in patients who have been unable to achieve adequate control with first- or second-line therapy. Although initially used for patients with T2DM with BMI >35 kg/m^2 (with comorbidities) or with BMI >40 kg/m^2, this approach has been used more recently for patients with BMI <35 kg/m^2 as well. Some clinical researchers believe that BMI-based criteria for bariatric surgery are not adequate for determining eligibility in patients with diabetes. Therefore, most obesity or bariatric surgery professional societies have added the term "metabolic" to their organization names.

Many clinicians (i.e., endocrinologists, metabolic surgeons) distinguish between bariatric and metabolic surgery because the goals of the surgery differ, although the same procedures are used to accomplish those goals. The goal of bariatric surgery is typically achieving weight loss, while the goal of metabolic surgery is achieving metabolic stability and diabetes remission. This difference has contributed to a paradigm shift in bariatric surgery for T2DM from interventions directed at obesity alone to restoring metabolic imbalances and has loosened the patient eligibility criteria from a focus purely on high BMI. A consensus is building that the metabolic improvements occurring after surgery often precede weight loss in patients who are obese, and the improvements have occurred even in patients with a BMI lower than that used to define obesity.

Metabolic surgeries for T2DM are classified as purely restrictive, restrictive/malabsorptive, or purely malabsorptive. Purely restrictive procedures limit food consumption, while purely malabsorptive procedures reduce food absorption.[92,93] Today, most often the procedures are done laparoscopically; however, laparoscopic surgery may be difficult in patients with very high BMIs, intra-abdominal adhesions, or hernias. Therefore, surgery may still be performed as an open procedure.[94]

A purely restrictive procedure is adjustable gastric banding, in which surgeons place a band around the upper part of the stomach. This method is less invasive than some other metabolic surgeries, and the resulting pouch for food is smaller and empties into the lower stomach without bypassing the foregut. Gastric banding has been reported to be associated with excess weight loss of more than 30% (as much as 70%) and T2DM resolution (or improvement) in as many as 80% of patients in some studies.[92,95] Another restrictive procedure is the sleeve gastrectomy. This method is a vertical gastrectomy, an irreversible procedure in which a large portion of the stomach is surgically excised.[96]

Roux-en-Y gastric bypass (RYGB) surgery, a restrictive and malabsorptive procedure, is the most common type of metabolic surgery.[96] The procedure is primarily restrictive, although it has both restrictive and malabsorptive features.[95] The surgeon partitions the stomach to form a small, 30 mL pouch where food will enter.[95] The surgeon then connects the distal small intestine to this gastric pouch. This connection creates the "Roux," or alimentary limb of the Y-shaped construction. Next, the surgeon connects the duodenum portion of the upper small intestine to a distal section of the small intestine. This construction results in the bypass of the duodenum and upper jejunum and creates the second limb of the "Y."[95,97] Biliopancreatic diversion with or without duodenal switch is

another restrictive and malabsorptive procedure. Surgeons perform a distal gastric resection and create a stapled closure of the duodenal stump to result in a stomach volume of around 300 mL. With the duodenal switch, the surgeon performs a proximal gastric resection leaving the pylorus to control food drainage. Food and digestive nutrients mix in the remaining 50 cm of the bowel.[95,96]

A purely malabsorptive procedure is the jejunoileal bypass, an ileal interposition linked to a diverted sleeve gastrectomy. The procedure connects the ileum, the lowest part of the small intestine, to the proximal intestine to keep digestive nutrients away from the bowel, in essence limiting small intestine length and absorptive surface area.[95] Another malabsorptive procedure is the duodenojejunal bypass. This is a stomach-sparing bypass in which surgeons partially transect the duodenum 2 cm distal to the pylorus and perform duodenojejunal anastomosis to manipulate the intestine.[96]

Clinical Trials: Many trials have been published reporting results that include patients with T2DM who are not considered to be morbidly obese. In a trial (n=31) reporting 3-year followup in February 2013, Lanzarini and colleagues reported on patients with T2DM and mild obesity:[98]

> This prospective clinical trial includes patients with T2DM with a body mass index (BMI) between 30 and 35 kg/m^2 who underwent laparoscopic RYGBP [Roux-en-Y gastric bypass] from July 2008 through October 2010. Thirty-one patients were included in the study, 15 men and 16 women, with an average age of 48.7 ± 8.6 years. The average time since onset of T2DM was 5.8 years. The average postoperative follow-up was 30.4 months. The average preoperative blood glucose and glycosylated hemoglobin were 152 ± 70 mg/dl and 7.7 ± 2.1 %, respectively. All of them were using oral hypoglycemic agents, and four patients were insulin dependent. Only one patient had a postoperative complication (hemoperitoneum). At 36 months follow-up, the average BMI decreased to 24.7 kg/m^2, all patients (31) showed improvement in their glycemic control, and 29 of them (93.6 %) met the criteria for remission of T2DM in the last control. Laparoscopic RYGBP is a safe and effective procedure that improves glycemic control in patients with T2DM and mild obesity at midterm follow-up.

In July 2012, Cohen and colleagues published results from a study assessing RYGB in 66 patients with T2DM and mild obesity, as follows.[99]

> For up to 6 years following RYGB, durable diabetes remission occurred in 88% of cases, with glycemic improvement in 11%. Mean HbA(1c) fell from 9.7 ± 1.5 to $5.9 \pm 0.1\%$ ($P < 0.001$), despite diabetes medication cessation in the majority. Weight loss failed to correlate with several measures of improved glucose homeostasis, consistent with weight-independent antidiabetes mechanisms of RYGB. C-peptide responses to glucose increased substantially, suggesting improved β-cell function. There was no mortality, major surgical morbidity, or excessive weight loss. Hypertension and dyslipidemia also improved, yielding 50-84% reductions in predicted 10-year cardiovascular disease risks of fatal and nonfatal coronary heart disease and stroke.

Manufacturer and regulatory status: Surgical procedures are not subject to marketing approval by FDA; however, the bands used in gastric banding (e.g., Lap-Band, Realize) are subject to FDA regulation. Searches identified four manufacturers that distribute and market devices used for gastric band procedures.[100-103] Commercially available technologies for metabolic surgery include:

- Lap-Band Adjustable Gastric Band by Allergan, Inc. (Irvine, CA)[100]

- Realize adjustable gastric band by the Ethicon Endo-Surgery unit of Johnson & Johnson (New Brunswick, NJ)[101]
- Heliogast HAGA, HAGE Gastric Band by Helioscopie (Vienne, France)[102]
- Midband Adjustable Gastric Band by Médical Innovation Développement (Dardilly, France)[103]

Of two devices that FDA has approved, only one has an indication that includes patients with a BMI <35 kg/m^2, the Lap-Band.[104,105] In June 2001, Allergan received FDA marketing approval through the PMA application process for the Lap-Band Adjustable Gastric Banding System.[106] The device is indicated for use in weight reduction for severely obese patients with BMI of at least 40 kg/m^2 or BMI of at least 35 kg/m^2 with one or more severe comorbidity. Since the original PMA, 26 supplements have been submitted involving process changes, changes in design, postmarket study modifications, and a change in the labeled indication. In February 2011, the Lap-Band received approval for the labeling change, which indicated its use for weight reduction for patients with a BMI ≥40 kg/m^2 or ≥30 kg/m^2 with one or more obesity-related comorbidity.[104]

Diffusion and costs: Although metabolic surgery has been performed for many years for the obese population with T2DM, this option remains relatively new for nonobese patients with T2DM. The increase in publication of studies on this population suggests its use is increasing. The U.S. Centers for Disease Control and Prevention estimated the direct and indirect diabetes costs in the United States for 2007 at $174 billion; thus, a procedure that could induce permanent remission could affect and possibly reduce long-term costs.[107]

Metabolic surgery is costly and complex. The average total cost reported for lap-band surgery ranges from $17,000 to $30,000, and the average reported cost for gastric bypass ranges from $20,000 to $35,000.[108] These costs generally include preoperative lab work, x-ray fees, cardiac screening, and anesthesia, hospital, and surgeon fees. Costs vary by procedure, operating surgeon, location of health care provider, and length of recovery. Postsurgery costs are additional and may include dietary planning, a fitness regimen, potential behavioral modification, and lifetime nutritional supplementation.

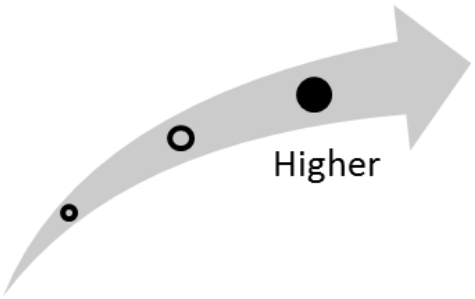
The U.S. Centers for Medicare & Medicaid Services has a national coverage determination titled "Surgery for Diabetes" that states, "Medicare currently covers bariatric surgery for persons with T2DM and BMI >35…and are non-covered for Medicare beneficiaries who have a BMI <35 and T2DM."[109] Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 10 outlining coverage, with only Wellmark having no policy listed. The other 10 have policies that indicate they provide coverage for surgical treatment of obesity when the patient has BMI >40 kg/m^2 or BMI >35 kg/m^2 with comorbidities.[110-119] Only HealthPartners' policy comments on BMI <35 kg/m^2, stating "weight loss surgery is not covered for BMI less than 35."[115]

Clinical Pathway at Point of This Intervention

T2DM typically occurs later in life, although incidence in a younger population has been growing as a result of the obesity epidemic. Initial treatment includes dietary modification, exercise, and self-monitoring of blood glucose. First-line drug therapies include biguanides, sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and dipeptidyl peptidase-4 inhibitors. Some patients require combination drug therapy of agents with different mechanisms of action for additive therapeutic effects and better glycemic control. Despite the availability of oral antidiabetes drugs, many patients do not achieve treatment goals and require additional therapy with an injected antidiabetes agent: subcutaneous insulin or a GLP-1 agonist.[74] Bariatric surgery would

provide another treatment option for T2DM in patients who are obese and not achieving adequate blood glucose control with medication or insulin.

Figure 4. Overall high-impact potential: metabolic (bariatric) surgery for resolution of type 2 diabetes in mildly obese and nonobese patients



Experts commenting on this intervention agreed on the potential of this surgery to address the unmet need. Overall, the experts opined that metabolic surgery has potential to improve health outcomes in patients with T2DM and induce remission for a majority of patients in the short term. However, some experts questioned the long-term success of the procedures and cited a need for more data to address this question. Experts commented that this intervention should be used as a last resort for patients who cannot achieve their target glucose goals with other, less drastic treatment options. Some experts noted that patients may be willing to undergo surgery if the need for lifelong medication adherence is eliminated and T2DM is resolved. Experts generally agreed on the potential of this intervention to disrupt patient management, citing a shift from medication to surgery. The surgery could increase short-term costs of T2DM treatment, but might offset costs over time if long-term remission can be achieved. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.[120-125] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for potentially curative treatments such as metabolic surgery, the majority of experts agreed. One expert with a health systems perspective noted, "The burden of T2DM and obesity is great. If life alteration or medication fail, surgery is an option to get off of meds and reduce the comorbidities associated with each."[120] Experts also generally agreed on the potential of this intervention to improve patient health outcomes. One research expert opined, "Overall, I think that metabolic surgery is a severe and extreme treatment option for most patients with diabetes, but a large proportion of those who have undergone the procedure seemed to have benefitted."[122] However, some experts noted the need for more long-term efficacy data to understand whether remission is maintained. A clinical expert opined, "A longer follow-up period may also be necessary to really assess for disease recurrence at 5 years."[124]

Acceptance and adoption: The likelihood of clinician acceptance of metabolic surgery was a matter of mixed opinion. Although some experts agreed on the potential for clinician acceptance, others commented that this intervention would likely be used only as a last resort. One research expert opined, "Metabolic surgery seems to be a serious and severe, extreme form of treatment relative to alternative options. Especially when you consider that lifestyle changes alone should be able to resolve the disease. I believe clinicians will adopt metabolic surgery only as a last resort, and

for patients who they deem ideal candidates."[122] Alternatively, another expert with a research perspective noted, "Clinicians will accept it but will be concerned about potential side effects."[123] Additionally, one clinical expert opined, "The bariatric surgery market for morbidly obese patients has remained plateaued for the past 1-3 years despite ever increasing literature to support the efficacy and safety of metabolic procedures," and thought the same might be true for its use for treating T2DM in nonobese patients if made more widely available.[124]

Although comments regarding patient acceptance were mixed, experts were generally more optimistic about patient acceptance. Some cited the lack of long-term efficacy studies as potential barriers for clinicians and patients alike. However, one health systems expert opined, "In our quick fix society, patients often want this procedure as a way of helping them achieve their goals."[125]

Health care delivery infrastructure and patient management: This intervention is a potentially disruptive treatment option compared with lifestyle management and pharmacotherapy, most experts thought. One research expert commented, "Patients who have diabetes are typically treated with lifestyle management, one or many pharmacotherapeutic options, and/or insulin therapy. Adding an invasive surgical procedure to the list of treatment options would be a large disruption to healthcare delivery, especially considering many of these procedures are performed inpatient. Relevant staff will also need training in the procedures, particularly in nonobese patients."[122]

One health systems expert opined that this option represented a "huge disruption in lifetime care patterns."[120] Another research expert elaborated, "Patients with diabetes will have a surgical adjunct (and possibly alternative) to their current treatment regimens, which typically include lifestyle intervention, pharmacotherapy, and/or exogenous insulin. This would likely increase patient volume at healthcare facilities. However, long-term, these procedures could reduce the burden of treating diabetes if they prove safe and effective."[122] Conversely, one clinical expert commented that patient management would not be disrupted until metabolic surgery is fully endorsed by numerous medical societies.[124]

Health disparities: Most experts agreed when commenting on the potential for this intervention to widen health disparities. One research expert commented, "Obesity is more prevalent in minority communities, and also is more prevalent in poorer communities. However, these communities may not have as much access to bariatric surgery, and so it could widen disparities."[123] Some experts cited limited access due to financial reasons. One research expert noted, "I would expect that given the cost for metabolic surgical procedures, and the fact that these procedures are generally only covered for certain indications, access to treatment could be limited to only those patients able to afford it."[122]

Diabetic Macular Edema Intervention

Fluocinolone Acetonide Implant (Iluvien) for Treatment of Diabetic Macular Edema

Unmet need: The standard treatment for diabetic macular edema (DME) is laser photocoagulation, and this treatment cannot reverse vision loss that has already occurred. Vision loss continues to progress in some patients despite treatment.[126-128] Additional vision loss is also a risk associated with the laser photocoagulation procedure.[126]

Recently, intravitreal injection has become a standard treatment for DME. Once such injected agent is ranibizumab, which FDA approved in 2012 for treating DME; it purportedly functions as an anti-angiogenic agent. Additionally, because inflammation is thought to play a role in DME, off-label corticosteroid injections have been used by some retinal physicians to treat DME. Both anti-angiogenic and corticosteroid treatments require ongoing treatment involving multiple intravitreal injections per year for effective treatment.[129-131] Thus, interest exists in developing more convenient and safer intravitreal therapies for patients with DME. An intravitreal insert that provides a sustained release of the corticosteroid fluocinolone acetonide (Iluvien®) is being developed as a potential long-term treatment for DME.

Intervention: Iluvien is a sustained-release, intravitreal corticosteroid insert intended for treating DME.[132] The insert consists of 190 mcg of the corticosteroid fluocinolone acetonide in a tiny, cylindrical, polyimide tube designed to provide sustained drug release into the eye. The insert is delivered by intravitreal injection to the back of the eye with a 25-gauge needle, a needle size that purportedly allows natural physiologic sealing of the injection site. Iluvien is designed to have a therapeutic effect for up to 36 months through stable, long-term release of fluocinolone acetonide into the eye.[132,133] In clinical trials, two doses of Iluvien were administered to patients with DME: a high dose with an initial release rate of 0.45 mcg per day or a low dose with an initial release rate of 0.23 mcg per day.[132]

Clinical trials with Iluvien have demonstrated that patients with persistent DME responded well to Iluvien treatment despite poor responses to other treatments and that patients who had had DME for 3 years or longer responded better to treatment than those who had had DME for less than 3 years.[134] The exact mechanism for this improved visual acuity after treatment in patients with longer-duration DME is not known. Investigators hypothesize that chronic edema may exacerbate the inflammation that occurs in DME and that corticosteroids exert a therapeutic effect by modulating vascular permeability via several mechanisms including inflammatory cell inhibition, inflammatory cytokine downregulation, and stabilization of cell membranes and tight junctions.[129,134]

Clinical trials: In a February 2013 analysis of two multinational trials in patients with DME previously treated with macular laser photocoagulation, authors reported the following:[135]

> Fluocinolone acetonide intravitreal implant 0.2 μg/day was significantly more efficacious than sham injection in improving visual acuity. At 24 months post injection, 29 % of fluocinolone acetonide intravitreal implant 0.2 μg/day recipients had an improvement in the best-corrected visual acuity (BCVA) letter score of ≥15 compared with 16 % in the sham injection group ($p = 0.002$) [primary endpoint]. Treatment benefit was most evident in the subgroup of patients whose duration of [DME] was ≥3 years. In this subgroup at 36 months, 34 % of fluocinolone acetonide intravitreal implant 0.2 μg/day recipients had an increase in the BCVA score of ≥15, compared with 13 % of sham injection recipients ($p < 0.001$). Fluocinolone acetonide intravitreal implant recipients also had generally greater benefits than sham injection recipients on secondary endpoints. In patients who were phakic in the study eye at baseline, cataracts occurred in 82 % of fluocinolone acetonide

intravitreal implant 0.2 μg/day recipients and 51 % of sham injection recipients. Overall, 37 % and 12 % of patients in the fluocinolone acetonide intravitreal implant and sham injection groups developed raised intraocular pressure (IOP), which was generally controlled with IOP-lowering drugs.

Two Campochiaro and collaborators publications reported on the same phase III clinical trial (FAME™), which evaluated 953 patients over 36 months. The first listed trial (June 2012) reported the following data from the completed 36-month trial:[134]

> At month 36, the percentage of patients who gained ≥15 in letter score using the last observation carried forward method was 28.7% (low dose) and 27.8% (high dose) in the FAc [fluocinolone acetonide] insert groups compared with 18.9% (P = 0.018) in the sham group, and considering only those patients still in the trial at month 36, it was 33.0% (low dose) and 31.9% (high dose) compared with 21.4% in the sham group (P = 0.030). Preplanned subgroup analysis demonstrated a doubling of benefit compared with sham injections in patients who reported duration of DME ≥3 years at baseline; the percentage who gained ≥15 in letter score at month 36 was 34.0% (low dose; P<0.001) or 28.8% (high dose; P = 0.002) compared with 13.4% (sham). An improvement ≥2 steps in the [ETDRS] retinopathy scale occurred in 13.7% (low dose) and 10.1% (high dose) compared with 8.9% in the sham group. Almost all phakic patients in the FAc insert groups developed cataract, but their visual benefit after cataract surgery was similar to that in pseudophakic patients. The incidence of incisional glaucoma surgery at month 36 was 4.8% in the low-dose group and 8.1% in the high-dose insert group."

The second Campochiaro trial (April 2011) reported the following data at month 24:[136]

> The percentage of patients with improvement from baseline ETDRS letter score of 15 or more at month 24 was 28.7 and 28.6 in the low- and high-dose insert groups, respectively, compared with 16.2 in the sham group (P = 0.002 for each). Benefit occurred for both doses compared with sham at 3 weeks and all subsequent time points. The mean improvement in BCVA letter score between baseline and month 24 was 4.4 and 5.4 in the low- and high-dose groups, respectively, compared with 1.7 in the sham group (P = 0.02 and P = 0.016). At all time points compared with sham, there was significantly more improvement in FTH (foveal thickness). Subjects requiring cataract surgery were more frequent in the insert groups, and their visual benefit was similar to that of subjects who were pseudophakic at baseline. Glaucoma requiring incisional surgery occurred in 3.7%, 7.6%, and 0.5% of the low-dose, high-dose, and sham groups, respectively."

These 24-month data were submitted in the manufacturer's original 2010 FDA NDA.

In August 2011, Pearson and colleagues published 3-year results from a 4-year, multicenter, randomized controlled clinical study that evaluated the safety and efficacy of fluocinolone acetonide intravitreal implants in eyes with refractory DME. Patients (196 eyes) were randomly assigned in a 2:1 ratio to receive the implant or standard of care (SOC; additional laser or observation). The authors reported the following results:[137]

> Overall, VA [visual acuity] improved ≥3 lines in 16.8% of implanted eyes at 6 months (P=0.0012; SOC, 1.4%); in 16.4% at 1 year (P=0.1191; SOC, 8.1%); in 31.8% at 2 years (P=0.0016; SOC, 9.3%); and in 31.1% at 3 years (P=0.1566; SOC, 20.0%). The number of implanted eyes with no evidence of retinal thickening at the center of the macula was higher than SOC eyes at 6 months (P<0.0001), 1 year (P<0.0001; 72% vs 22%), 2 years (P=0.016), and 3 years (P=0.861). A higher rate of improvement and lower rate of decline in DRSS [Diabetic Retinopathy Severity

> Score] occurred in the implanted group versus the SOC group at 6 months (P=0.0006), 1 year (P=0.0016), 2 years (P=0.012), and 3 years (P=0.0207). [IOP] ≥30 mmHg was recorded in 61.4% of implanted eyes (SOC, 5.8%) at any time and 33.8% required surgery for ocular hypertension by 4 years. Of implanted phakic eyes, 91% (SOC, 20%) had cataract extraction by 4 years.

Manufacturer and regulatory status: pSivida Corp. (Watertown, MA) develops minute, sustained-release, drug-delivery products designed to deliver drugs at a controlled and steady rate for months or years and licensed Iluvien to Alimera Sciences, Inc. (Alpharetta, GA). In June 2010, after completing the FAME study, the companies submitted an NDA to FDA for the low-dose formulation of the drug. The application was granted priority review status, but in December 2010, FDA requested that 36-month FAME data be delivered and that manufacturing, packaging, and product sterilization processes be reported before it would consider approval. The 36-month trial results were provided to FDA in May 2011. In November 2011, the company stated the following about the complete response letter it received from FDA:[138]

> FDA stated that it was unable to approve the ILUVIEN NDA because the NDA did not provide sufficient data to support that ILUVIEN is safe and effective in the treatment of patients with DME. The FDA stated that the risks of adverse reactions shown for ILUVIEN in the FAME® Study were significant and were not offset by the benefits demonstrated by ILUVIEN in these clinical trials. The FDA has indicated that Alimera will need to conduct two additional clinical trials to demonstrate that the product is safe and effective for the proposed indication.

The company met with FDA in June 2012, and based on the outcome of that meeting, declared intentions to resubmit data from two previously completed phase III trials (FAME studies) to address FDA's concerns.[139] In May 2013, Alimera announced that FDA had received its NDA resubmission and set October 17, 2013, as the therapy's new Prescription Drug User Fee Act (PDUFA) date.[140] However, after initial review, FDA scheduled an advisory committee meeting for January 27, 2014, to address clinical and statistical deficiencies. FDA also indicated that the manufacturer would need to submit new clinical trial data to address concerns of risk and safety profiles.[141] pSivida Corp. announced in April 2014 that FDA accepted Alimera Science's resubmission and set a PDUFA date of September 26, 2014.[142] Iluvien is being marketed in Austria, France, Germany, Italy, Portugal, Spain, and the United Kingdom[143] for treating "DME considered insufficiently responsive to available therapies."[144]

Diffusion and costs: If approved in the United States, the drug would compete with laser photocoagulation and off-label corticosteroid injections for DME;[129-131] these treatments cannot reverse vision loss that has already occurred, and vision loss continues to progress in some patients despite those treatments.[126-128] Additional vision loss is also a risk associated with laser photocoagulation.[126] Fluocinolone acetonide could also complement laser therapy and might be potentially more convenient and safer than corticosteroid therapy, because it would not require ongoing intravitreal steroid injections; thus, patients might find it a more appealing option.

Costs for the Iluvien implant in the U.S. market are not yet known. However, some industry analysts expect the product to be priced comparably to Retisert®, a fluocinolone acetonide ophthalmic implant that is FDA-approved to treat uveitis. According to ECRI Institute's PriceGuide Database, the price of a single Retisert implant is about $18,250. The product is designed to deliver its drug payload over 30 months.[145] Other cutting-edge ophthalmic treatments, such as pegaptanib (Macugen®) injections, which are indicated to treat wet age-related macular degeneration, cost about $8,000–$9,000 per patient per year (approximately $1,000 per injection).[145]

The fluocinolone acetonide implant will also probably compete with ranibizumab (Lucentis®), a vascular endothelial growth factor (VEGF) inhibitor approved for treating DME with monthly

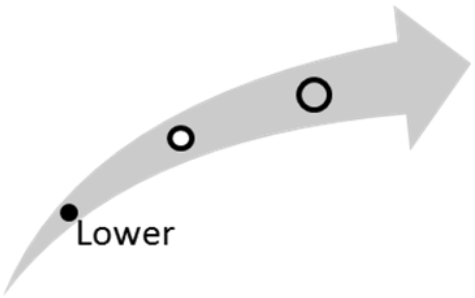
intravitreal injections.[146] Ranibizumab costs an estimated $2,000 per vial with the use of a coupon.[147]

Additional DME treatment options under investigation include other corticosteroid medications and anti-VEGF agents. Ozurdex® (formerly Posurdex) is a biodegradable intravitreal implant that releases low doses of the corticosteroid dexamethasone over the course of 4 months.[148,149] The drug is undergoing phase III trials for treating DME and has been approved by FDA for treating uveitis and macular edema after central and branch retinal vein occlusion. Bevacizumab (Avastin®) and pegaptanib (Macugen®) are anti-VEGF (antiangiogenic) drugs typically used in cancer treatment and age-related macular degeneration; in clinical trials, researchers are testing the efficacy of small doses for treating DME.[150] In one recently completed phase IV study, researchers studied the efficacy of combining Ozurdex with bevacizumab for treating DME.[151] Bevacizumab is reportedly used widely for off-label treatment of ophthalmic conditions, including DME, as a significantly less-expensive alternative to ranibizumab.[152-155] However, some researchers report that intravitreal injections of bevacizumab are associated with a significantly higher rate of serious adverse events (because of the dose-preparation requirements for ophthalmic administration), which could pose an additional cost burden to treat. In one Canadian retrospective study, subjects who received bevacizumab for ophthalmic indications were 12 times as likely to develop severe intraocular inflammation after each injection as were patients who received ranibizumab injections.[156]

Clinical Pathway at Point of This Intervention

A patient who presents with symptoms suggesting DME undergoes a history and physical examination pertaining to diabetes history, vision and eye disease history, and other risk factors (i.e., older age, poor glucose control, pregnancy, hypertension, and increased lipid levels).[157] Using a high-magnification ophthalmoscope, the ophthalmologist can identify the retinal thickening that indicates macular edema. Yellow exudates and poor visual acuity may also be detected. DME treatment focuses on glycemic control, optimal blood pressure control, and macular focal/grid laser photocoagulation. Standard therapy has been laser photocoagulation and use of ranibizumab or off-label bevacizumab.[157]

Figure 5. Overall high-impact potential: fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema



A significant unmet need exists for effective DME treatments, experts agreed. They opined that this implant has the potential to improve patient health outcomes, citing increased medication adherence. However, several experts expressed concerns regarding potential adverse events, including cataracts and increased intraocular pressure. Experts generally wanted to see more data, including comparative trials with monthly intravitreal injections of ranibizumab. Clinician acceptance is likely to be moderated by the potential for adverse events, experts thought; but patients would be more likely to accept this intervention for reasons of convenience. Based on this input, our overall assessment is that this intervention is in the lower high-impact-potential range.

Results and Discussion of Comments

Five experts, with clinical, research, and health systems and administration backgrounds, provided perspectives on the fluocinolone acetonide implant.[73,158-161] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: DME is one of the leading causes of blindness and an important unmet need exists for safe and effective therapies for patients with this condition, most of the experts agreed. However, one research expert noted that standard DME therapy is available through laser photocoagulation, corticosteroids, or anti-VEGF therapies, making this new intervention just another treatment option.[73]

Most experts commenting on this intervention questioned its potential to improve patient health outcomes, citing safety concerns and limited efficacy data. One research expert commented, "The one study that compared Iluvien with SOC [standard of care] reported no significant difference in efficacy at 3 years. However, IOP ≥30 mmHg was recorded in 61.4% of implanted eyes at any time and 33.8% required surgery for ocular hypertension by 4 years."[158] The same expert representing a research perspective opined that this intervention could potentially improve patient health outcomes by improving patient adherence.[158]

Acceptance and adoption: Experts opined that clinician acceptance would likely be limited by the potential for adverse events, including cataracts and glaucoma. One research expert opined, "Clinicians will take into consideration this intervention because of the single injection vs multiple injections of other drugs. However, the high incidence of cataracts and the absence of long-term data might cause some clinicians to not use Iluvien in young patients."[73]

Experts generally agreed that patient acceptance may be limited by the potential for adverse events, although some would be willing to accept the associated risks if this treatment proves to be effective. One research expert commented, "There is a greater significance of developing cataracts; however, surgeries to remove cataract are highly successful and suspect that developing cataracts will be acceptable to patients for Iluvien implants will prevent/slow down the progression of DME and blindness."[160]

Health care delivery infrastructure and patient management: Experts agreed that the fluocinolone acetonide implant would not disrupt health care delivery infrastructure, citing the potential for fewer physician-office visits. Experts did not anticipate a major impact to patient management, either. Most noted the similarities of this therapy's administration with intravitreal injections. However, some experts expressed concerns about the potential for increased physician office visits because of adverse events. One research expert opined, "Based on results of clinical trials, [it] would increase numbers of procedures performed to correct cataracts and elevated intraocular pressure (IOP)."[158]

Health disparities: Most experts agreed that this intervention would not be likely to affect health disparities. One research expert opined that the administration schedule for the fluocinolone acetonide implant could potentially provide better access to treatment for some patients compared with DME therapies that require more frequent intravitreal injections (e.g., anti-VEGF therapies).[73] This expert also thought that the cost of the implant could limit access to certain populations, "If priced similar to Retisert ($18,250), it might be an option only for those with high economic status and/or those with access to health insurance that grant coverage."[73]

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